بسم الله الرحمن الرحيم

In The Name Of ALLAH

The Most Gracious, The Most Merciful

Armed Forces College of Medicine

AFCM

Treatment Of Diabetes Mellitus

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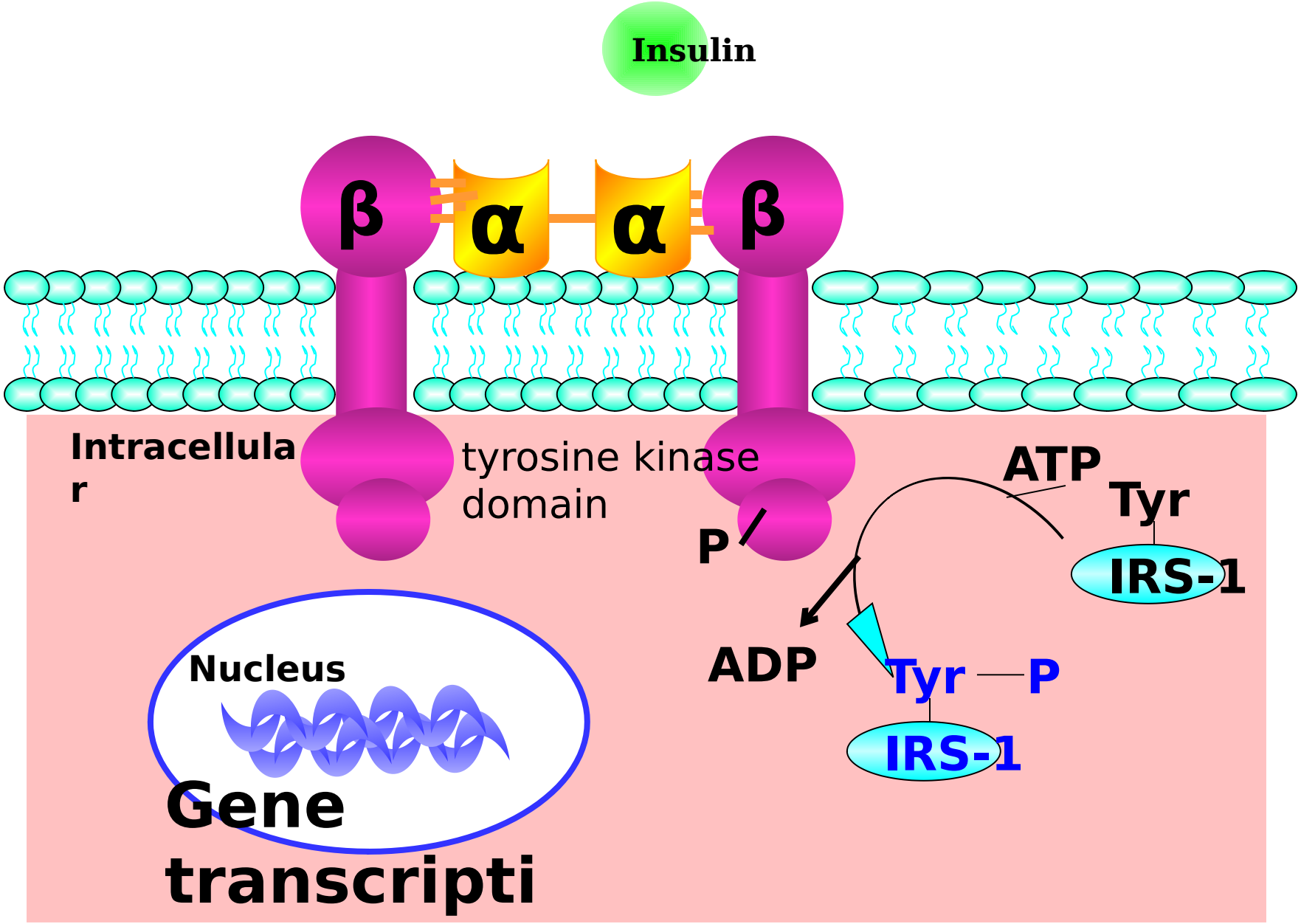
Diabetes

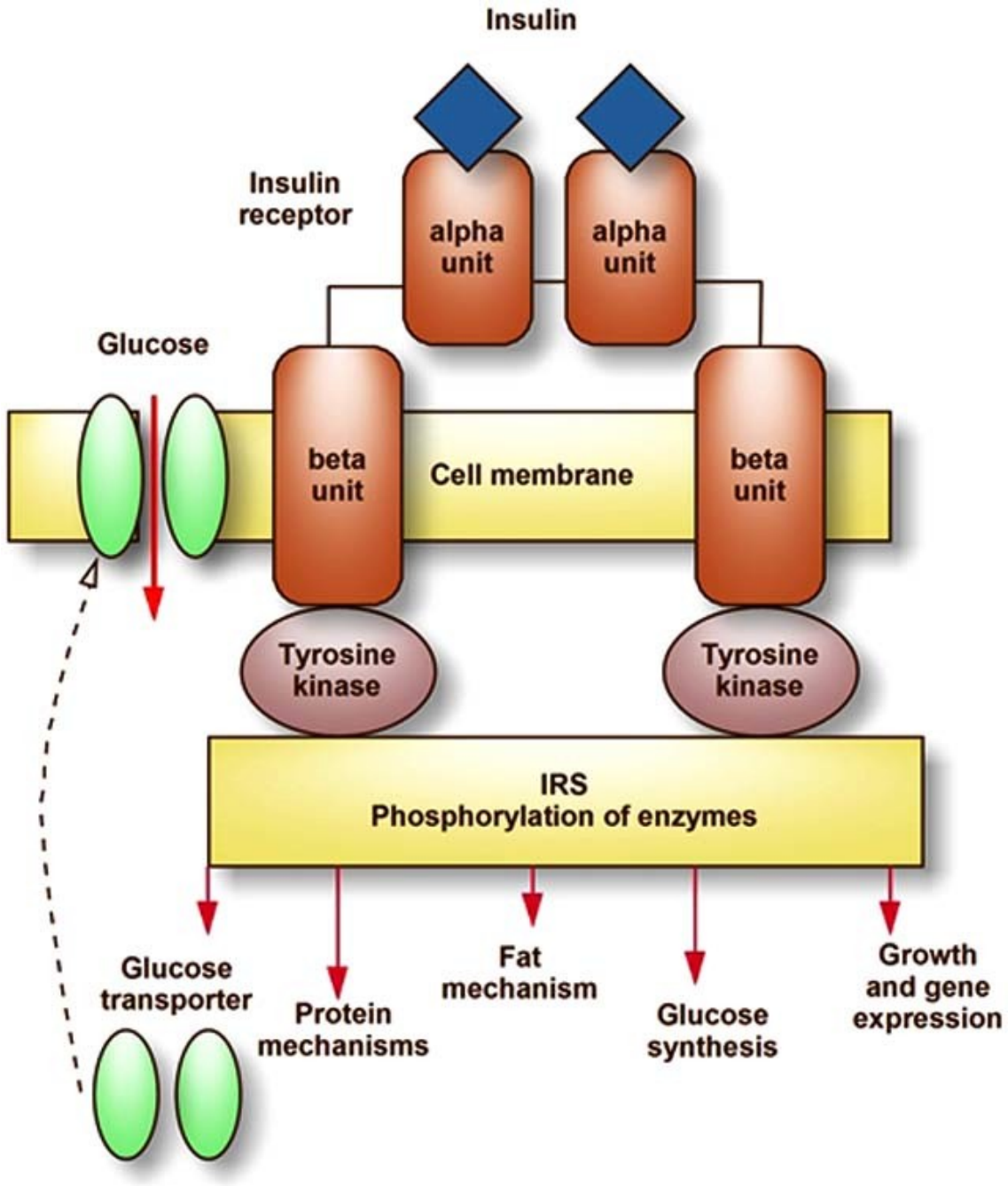
INTENDED LEARNING OBJECTIVES (ILO)

By the end of this lecture the student will be able to:

1. Identify the mechanism of action of Insulin
2. Explain the adverse effects of insulin preparations
3. Outline a plane of therapeutic drug management of emergency cases in diabetes mellitus
4. Identify the preparations of the antidiabetic drugs
5. Explain the drug - drug interactions of the antidiabetic drugs
6. Compare between incretin mimetics &

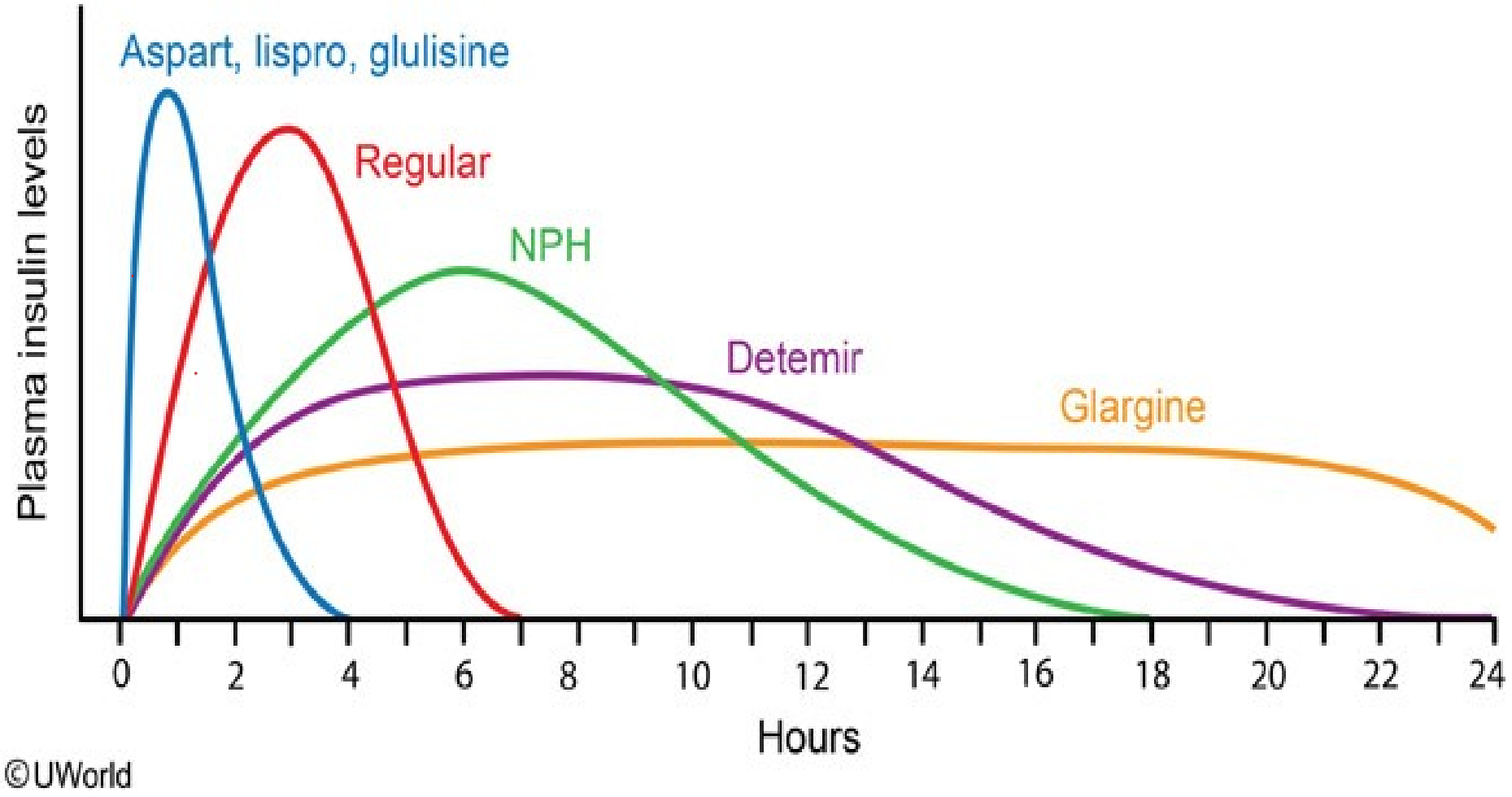
Insulin Receptor




Insulin
Insulin receptor
alpha unit
alpha unit
Glucose
beta unit
Cell membrane
beta unit
Tyrosine kinase
Tyrosine kinase
IRS
Phosphorylation of enzymes
Glucose transporter
Protein mechanisms
Fat mechanism
Glucose synthesis
Growth and gene expression

Type of preparation	Onset	Peak	Duration
1) Ultrashort Acting **Insulin Lispro** **Insulin Aspart**	5-15 min	30-90 minutes	4-6 hrs
2) Short Acting **Crystalline Zinc Insulin (soluble, *regular*)**	30-60 min	2-3 hours	6-8 hrs
3) Intermediate Acting **Isophane (NPH= neutral protamine hagedorn)**	2-4 hours	4-10 hrs	Up to 18 hrs
4) Long Acting **Insulin Glargine** **Insulin Detemir**	2-4 hours 1-2 hours	**No peak** **No peak**	Up to 24 hrs 16-24 hrs

Pharmacokinetic profiles of common insulin preparations



Regimens of insulin therapy

A. Split-mixed regimen: Regular + NPH insulin

dose split to 2 parts; 2/3 given 30 min before breakfast, 1/3 before supper to prevent overnight hyperglycemia.

B. Multiple daily injections:

insulin glargine given to achieve a more stable basal activity. Regular insulin must be given in three premeals injections (30 min prior to each meal).

- **Lispro insulin Have a shorter duration of action than regular insulin and so less risk of postprandial hypoglycemic events**

- **The most common premixed insulin** injection:

  70% NPH insulin and 30% regular insulin

  it must ***never be injected IV ???***

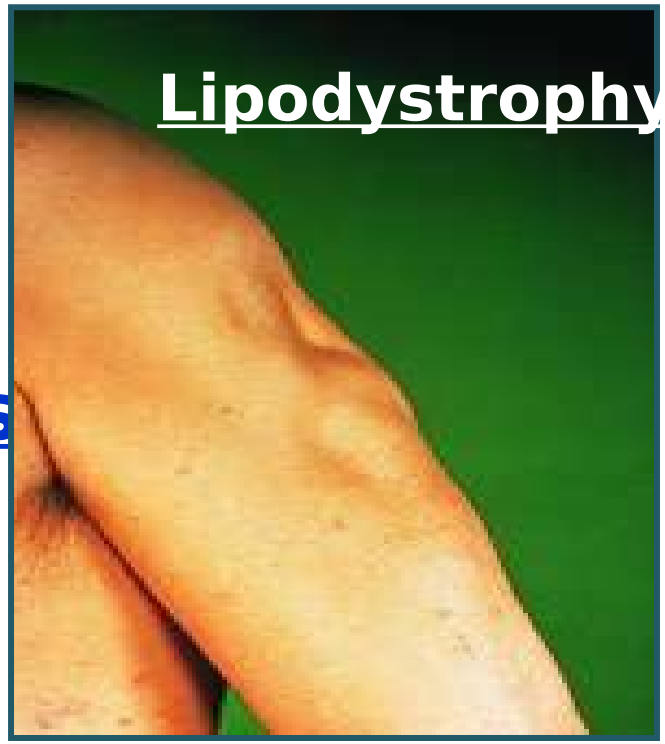
- **insulin glargine cause less nocturnal hypoglycemia and less weight gain.**

Adverse Effects of insulin preparation

1) Hypoglycemia:

MOST **Serious** & **Common** in an overdose

2) Lipodystrophy.



3) Allergic reactions

(less common with human insulin)

4) Hypokalemia

1

The insulin receptor is a:

(a) Ion channel regulating receptor

(b) Tyrosine protein kinase receptor

(c) G-protein coupled receptor

(d) PPAR gama receptor

2

The most common adverse reaction to insulin is:

(a) Hypoglycaemia

(b) Lipodystrophy

(c) Urticaria

(d) Angioedema

3

Which of the following preparations can be administered intravenously in diabetic ketoacidosis?

(a) Regular insulin

(b) Isophane insulin (NPH)

(c) Insulin Glargine

(d) Insulin Zinc Suspension

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A 24-year-old woman with type 1 diabetes wishes to try tight control of her diabetes to improve her long-term prognosis. Which of the following regimens is most appropriate?

(a) Morning injection of mixed NPH and Insulin Glargine

(b) Evening injection of mixed regular and NPH Insulin

(c) Morning and evening injections of regular insulin

(d) Morning injection of Insulin Glargine and supplemented

by regular insulin injections pre-meals

(e) Morning injection of insulin lispro and evening injection of NPH insulin

Indications of insulin

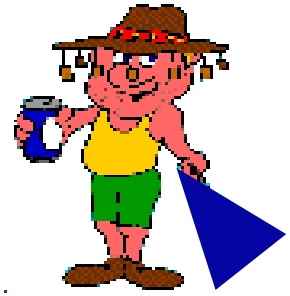
1) Type 1 (IDDM).
2) Diabetic ketoacidosis.
3) Type 2 (NIDDM) with:
   - Failed oral hypoglycemic ttt type 1
   - Temporarily: - infections.
                  - surgery.
                  - pregnancy.

Hypoglycemic coma

It is due to:

- Excess insulin or too little food intake or missing meal
- Too much muscular exercise.

Treatment



- If patient is **conscious** →Oral glucose or sweets.

- If patient in **Coma = Unconscious**

I.V. Glucose 25% → Life saving.

Glucagone 1 mg S.C. or I.M. if glucose is not available.

Diabetic ketoacidosis

- **Regular insulin I.V:**

  (20 units bolus then 0.1 unit /Kg /hr)
- **I.V fluids:**

  Saline then glucose 5% if glucose < 250 mg/dl
- **KCl** added to I.V fluids (if hypokalemia)
- **$NaHCO_3$ I.V** (if acidosis)

Anti-diabetic Drugs in Type 2 DM

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Anti-diabetic Drugs for type II DM

- **Insulin secretagogues** ***(Increase insulin release)***

  Sulfonylureas or Meglitinides (Glinides).

- **Insulin sensitizers** (***improve insulin action)***

  Biguanide (metformin)or ***ThiaZolidineDiones****(Glitazone*

- **Modify intestinal absorption of carbohydrate**

  Alpha-glucosidase inhibitor.

- **Incretin Mimetics & Enhancers**

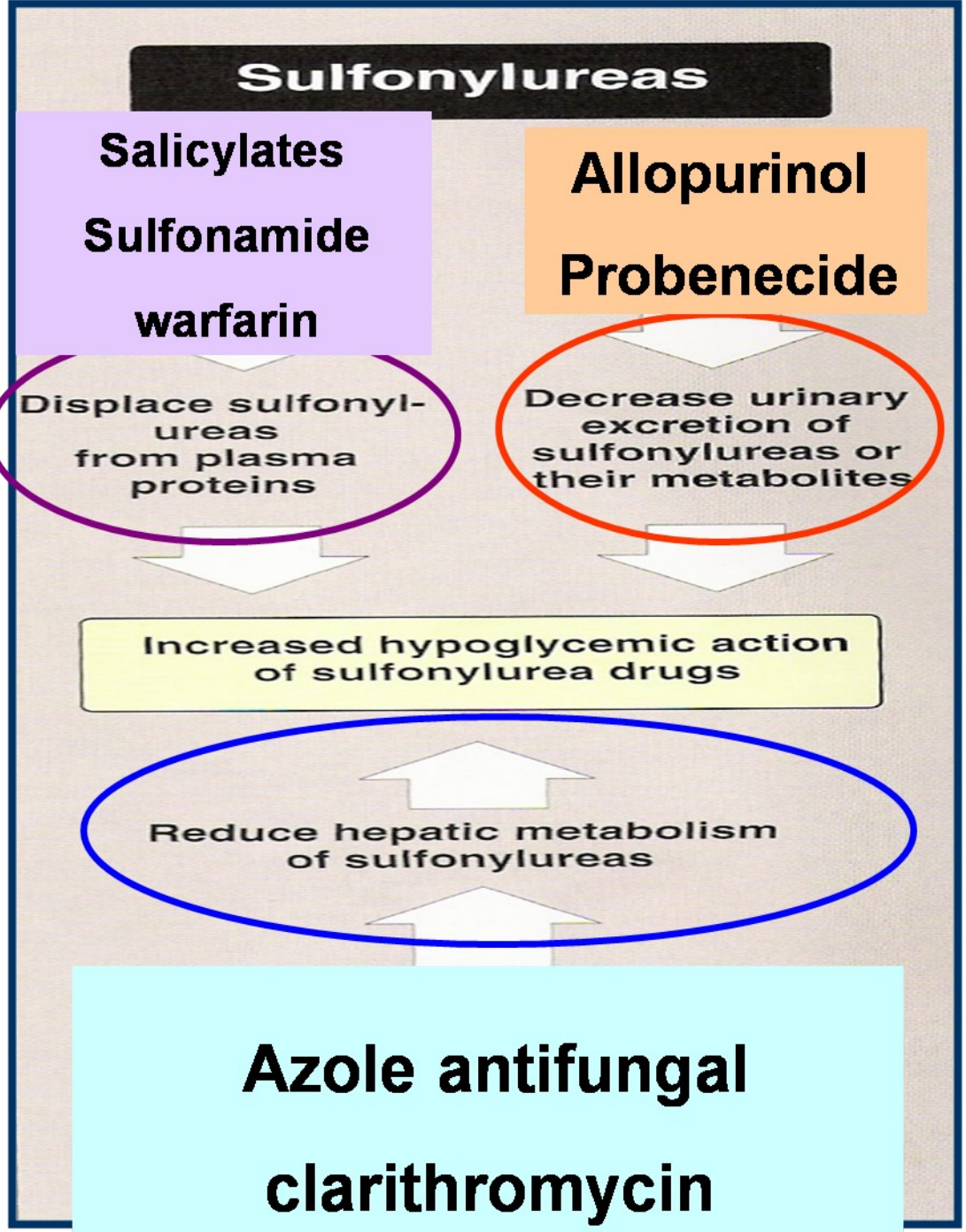
  GLP-1 analogs and DPP-4 inhibitors

- **Sodium-glucose cotransporter 2(SGLT2) inhibito**

  *Canagliflozin & Dapagliflozin****(Renal glucose reabsorptio***

Anti- diabetic drugs

classification	Drug	Mechanism of action	Main side effects	Route of admin.
Insulin secretagogues **Sulfonylureas**	***Glyburide*** **(may allowed in pregnancy)** **Glipizide or glimperide (safer in renal)**	•**Increase Insulin Release** **bind to SUR1 in β-cell pancreas blocks the ATP- dependent K channels depolarization Ca influx insulin release**	**Hypoglycemia.** **Weight gain.** **Drug interactions**	**oral**
Insulin secretagogues **Glinides (Meglitinides)**	**Repaglinide** **Nateglinide**	**Increase Insulin Release** **Short duration before each meal**	**Less hypoglycemia.** **Weight gain.**	**oral**
INSULIN SENSITIZERs **Biguanides** (**Euglycemic**)	**Metformin** (Anorexia **reduce weight)**	• Increase uptake and utilization of glucose by muscle & fat cells •**Decrease Glucose absorption** •**Decrease glucose production** by liver •**Increase insulin binding (to receptors) &action**	1) Nausea, vomiting & diarrhea. 2) Decrease Vit. B12 absorption 3) **Rarely fatal lactic acidosis** (In renal &hepatic dysfunction , HF, COPD & alcoholic)	**oral**
INSULIN	**Pioglitazon**	**Stim. PPAR -γ**	• **Hepatotoxicity(**	**oral**


Sulfonylureas
Salicylates
Sulfonamide
warfarin
Allopurinol
Probenecide
Displace sulfonyl-ureas from plasma proteins
Decrease urinary excretion of sulfonylureas or their metabolites
Increased hypoglycemic action of sulfonylurea drugs
Reduce hepatic metabolism of sulfonylureas
Azole antifungal
clarithromycin

classification	Drug	Mechanism of action	Main side effects	Route of admin.
α-Glucosidase Inhibitors	**Acarbose and Miglitol** **Miglitol is 5-6 times > potent**	Decreasing glucose absorption so decrease postprandial hyperglycemia	**flatulence, diarrhea, and abdominal cramping**.	oral
Incretin Mimetics **GLP-1 analog stimulate GLP-1 receptor (GLP-1-RA)**	•**Exenatide** •**Liraglutide** **(with CV Safety except in severe HF)**	↑ insulin release ↓ glucagon release Delay Gastric emptying ↓Appetite. ↓↓ ***weight***	•Risk of hypoglycemia with sulphonylurea	**S.C. injection**
Incretin Enhancers **DPP-4 inhibitor (DPP-4 i)**	• **Sitagliptin** • **Linagliptin (safer in renal)** (eliminated via	↑ insulin release ↓ glucagon release Delay Gastric	•Pancreatitis •**Saxagliptin** **↓cardiac contractility risk of HF**	oral

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Which of the following drugs is most likely to cause hypoglycemia when used as monotherapy in the treatment of type 2 diabetes?

(a)Acarbose

(b)Glyburide

(c) Metformin

(d) Miglitol

(e) Rosiglitazone

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Sulfonylureas are a primary mode of therapy in the treatment of

(a) Insulin–dependent (type 1) diabetes mellitus (DDM) patients

(b) Diabetic patients experiencing severe hepatic or renal dysfunction

(c) Diabetic pregnant women

(d) Patient with diabetic ketoacidosis

(e) Non-insulin-dependent (type 2) DM patients

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The hypoglycaemic action of sulfonylureas is likely to be attenuated by the concurrent use of

(a) Hydrochlorothiazid

(b) Propranolol

(c) Chloramphenicol

(d) Aspirin

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It is strongly recommended to measure (initially & periodically) the liver enzyme levels of patients on which of the following medication:

a) Metformin.
b) Miglitol.
c) Repaglinide
d) Pioglitazone
e) Exenatide.

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A 60-year-old male, alcoholic, treated for type II diabetes mellitus develops lactic acidosis. Which of the following oral antidiabetic agents might cause this adverse effect?

a) Glipizide .
b) Metformin.
c) Nateglinide.
d) Acarbose .
e) Glimepiride

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Metformin:

(a) Does not cause hypoglycemia even in large doses

(b) Should not be combined with glipizide

(c) Is contraindicated in obese NIDDM patients

(d) Causes release of insulin from the pancreas

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Select the drug which tends to reverse insulin resistance by increasing cellular glucose transporters:

(a)Glibenclamide

(b)Rosiglitazone

(c) Acarbose

(d) Prednisolone

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Which of the following is true about acarbose ?

(a) It increases absorption of glucose from intestine

(b) It produces hypoglycaemia in normal as well as diabetic subjects

(c) It limits postprandial hyperglycaemia in diabetics

(d) It raises circulating insulin levels

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The second generation sulfonylurea differ from the first generation one in that they

(a) Are more potent

(b) Are long acting

(c) Do not lower blood sugar in nondiabetics subject

(d) Are less prone to cause hypoglycaemic reaction

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Which of the following is an Incretin Enhancers which acts by inhibition of DPP-4 enzyme?

a) Glipizide
b) Liraglutide
c) Canagliflozin
d) Repaglinide
e) Linagliptin

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Which of the following is a GLP-1 receptor agonist and considered as Incretin Mimetics?

a) Glyburide
b) Liraglutide
c) Glipizide
d) Nateglinide.
e) Sitagliptin

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Which of the following inhibits Sodium-glucose cotransporter 2 and decreases the glucose reabsoption in the kidney ?

a) Glyburide
b) Exenatide
c) Canagliflozin
d) Nateglinide.
e) Saxagliptin

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Excessive use of Glimepiride will lead to:

(a) Diarrhea
(b) Prolonged hypoglycemia
(c) Tolerance to alcohol
(d) Acidosis
(e) Glycosuria

SUGGESTED TEXTBOOKS

1. Whalen, K., Finkel, R., & Panavelil, T. A. (2018) Lippincott's Illustrated Reviews: Pharmacology (7th edition.). Philadelphia: Wolters Kluwer

2. Katzung BG, Trevor AJ. (2018). Basic & Clinical Pharmacology (14th edition) New York: McGraw-Hill Medical.


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THANK YOU